(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 841 928 B1

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(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
25.09.2002 Bulletin 2002/39

(21) Application number: **96924083.7**

(22) Date of filing: **15.07.1996**

(51) Int Cl.[7]: **A61K 31/445**, A61P 25/00

(86) International application number:
PCT/GB96/01690

(87) International publication number:
WO 97/003673 (06.02.1997 Gazette 1997/07)

(54) SUSTAINED-RELEASE FORMULATION OF D-THREO-METHYLPHENIDATE

FORMULIERUNG VON D-THREO METHYLPHENIDAT MIT VERZÖGERTER FREISETZUNG

PREPARATION DE D-THREO-METHYLPHENIDATE A LIBERATION PROLONGEE

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **14.07.1995 GB 9514451**

(43) Date of publication of application:
20.05.1998 Bulletin 1998/21

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- **PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, vol. 40, no. 4, December 1991, USA, pages 875-880, XP000612226 ECKERMAN ET AL.: "Enantioselective Behavioral Effects of threo -Methylphenidate in Rats"**

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Description

Field of the Invention

[0001] This invention relates to a sustained-release formulation of methylphenidate.

Background of the Invention

[0002] Methylphenidate is a known drug. It is used primarily to treat hyperactive children. It is a controlled substance.

[0003] Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generally thought that d-threo-methylphenidate (abbreviated herein as dtmp) is the active material, and that its antipode (ltmp) is metabolised more rapidly.

[0004] Methylphenidate is often administered in a sustained-release formulation. For example, a coated tablet comprising racemic methylphenidate is administered, with a view to maintaining a therapeutically-effective level of the drug in circulation. This formulation does not provide satisfactory or reproducible dosing.

[0005] Srinivas *et al*, Pharmaceutical Research 10(1): 14 (1993), disclose a further disadvantage of known methylphenidate sustained-release formulations, i.e. that serum levels of the drug are increased by chewing. Many children chew tablets, and are therefore liable to receive an unnecessarily high dose of a controlled substance.

[0006] Patrick *et al*, Biopharmaceutics and Drug Disposition 10:165-171 (1989), describe the absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. It is suggested that the optimum dosage of methylphenidate for children is 0.5-0.7 mg/kg/day.

Summary of the Invention

[0007] The present invention is based on an appreciation of the fact that, although it is possible to provide a model of chiral drug distribution, and measure the concentration of individual enantiomers and their breakdown products in a subject, over time, this is a poor model for understanding the effectiveness of the enantiomers. Since, after an initial period, the sustained-release formulation should ideally release the active material as evenly as possible, the administration of a racemate, i. e. of two related compounds, takes no account of interaction between the enantiomers. According to this invention, it has surprisingly been found both that there is considerable interaction, and that dtmp provides relatively linear kinetics within the clinically effective dose range in a suitable model, and is therefore suitable for incorporation in a sustained-release formulation. The experiments and data on which this discovery is based are given below.

Description of the Invention

[0008] The dtmp that is used in this invention is substantially free of its antipode (ltmp), e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

[0009] The dtmp may be administered by the same means as is known for racemic methylphenidate, in a sustained-release formulation, e.g. a coated tablet. It may be administered in any other conventional sustained-release formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art.

[0010] Compositions of the invention may be administered for known purposes, e.g. the treatment of attention-deficient hyperactivity disorder (ADHD; this term is used herein to encompass attention-deficit disorder) in pre-pubertal children and in adults, as a stimulant in cancer patients treated with narcotic analgesics, and also for the treatment of depression (e.g. in AIDS patients), compulsive shopping disorder, narcolepsy and hypersomnia. By contrast to known formulations of methylphenidate, the present invention may have any or all of the following advantages: linear kinetics within the clinically effective dose range, the reduction of exposure to a controlled substance, reduced side-effects (which include anorexia, insomnia, stomach ache and headache), reduced abuse potential, reduced C_{max}, a reduced level of active material even when chewed, reduced patient variability, reduced interaction with ltmp or other drugs, and less variability between fed and fasted subjects.

[0011] By controlling the nature of the formulation, it is possible to control dissolution *in vitro*, and thus match or exceed the US National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C_{max}, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example, a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C_{max}.

[0012] The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns. Preferably, the serum level is at least 50% C_{max} after 8 hours and less than 25% C_{max} after 12 to 16 hours.

[0013] A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. It may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after admin-

istration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on administration, e.g. from microparticles to a gel, so that the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

[0014] It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. The various effects etc may be due to the use of dtmp and/or the absence of ltmp.

Comparative Pharmacodynamics of *d-threo*-methylphenidate and Racemate

[0015] The study design was based on that described by Aoyama *et al*, *J.* Pharmacobio-Dyn. 13:647-652 (1990). Male Wistar rats were dosed with methylphenidate hydrochloride or its d-isomer at nominal dose levels of

racemate: 1.5, 3, 4.5 or 6 mg base/kg body weight
d-isomer: 0.75, 1.5, 2.25 or 3 mg base/kg body weight

Blood samples were taken pre-dose, and 7 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4.5 h, 6 h, 8 h post-dose. The samples were centrifuged to separate the plasma. Plasma samples were assayed for dtmp, by liquid chromatography mass spectrometry.

[0016] The results are shown in the accompanying drawing. Figure 1 gives a comparison of the AUC (area under the curve) for values, obtained from plasma concentration of dtmp, versus time, for dtmp and methylphenidate (at equivalent dtmp quantities) dosed at a range of dtmp concentrations. Both curves show non-linear kinetics, evident as a point of disjunction in each curve. As the doses administered are increased, the quantity absorbed (i.e. AUC) increases in a linear fashion, until the disjunction, when the absorbed quantity is dramatically increased. This disjunction occurs within the clinically-relevant range (16-140 mg.h/ml in humans) for racemate dosing, but, surprisingly, is outside of this range for dtmp dosing.

[0017] This means that conventional dosing of the racemate, which involves increasing amounts of the drug, cannot be satisfactorily controlled. The possibility exists that a dosage will be given that is unnecessarily high.

[0018] Administration of dtmp has a surprising beneficial effect, in that a relatively linear dtmp AUC level in serum (lower curve) is achieved within the clinically-relevant range. The point of disjunction occurs outside the clinically-relevant range and, therefore, the flux of drug into and out of the circulatory system is more controllable. This makes dtmp suitable for incorporation in a sustained release formulation.

Claims

1. A sustained-release formulation of *d-threo*-methylphenidate (dtmp).

2. A formulation according to claim 1, which meets, or exceeds in terms of slower dissolution, the NF drug release profile for methylphenidate hydrochloride.

3. A formulation according to claim 1 or claim 2, which comprises less than 20 mg dtmp per unit dosage.

4. A formulation according to claim 3, which comprises less than 15 mg dtmp per unit dosage.

5. A formulation according to any of claims 1 to 4, selected from those comprising a soluble, erodable or otherwise modified coating, and those having an insoluble coating through which the dtmp passes, in use.

6. A formulation according to any of claims 1 to 5, in which the dtmp is micronised.

7. A formulation according to any of claims 1 to 6, which (on average) when administered to (a sample of) healthy subjects, exhibits a serum level of dtmp of at least 50% C_{max}, over a period of at least 8 hours.

8. A formulation according to claim 7, wherein the period is 8 to 12 hours.

9. A formulation according to claim 7 or claim 8, wherein the serum level is less than 25% C_{max} after 12 to 16 hours.

10. A formulation according to any of claims 1 to 9, which on administration to a healthy subject, exhibits C_{max} of 2 to 20 ng/ml at a dosage of at least 2 mg.

11. A formulation according to any of claims 7 to 10, wherein C_{max} is substantially unaffected by chewing.

12. Use of dtmp for the manufacture of medicament for use in treating a subject having a disorder capable of treatment using methylphenidate, a sustained-release formulation comprising dtmp in an amount sufficient to maintain a serum level of at least 50% of the maximum level, for at least 8 hours.

13. Use according to claim 12, wherein at least the initial dosage is less than 15 mg dtmp per day.

14. Use according to claim 12 or claim 13, wherein the subject is adult and the disorder is compulsive shopping disorder, narcolepsy or hypersomnia.

15. Use according to claim 12 or claim 13, wherein the disorder is attention-deficit hyperactivity disorder.

16. Use according to any of claims 12 to 15, wherein said amount is less than 1 mg/kg/day.

17. Use according to claim 16, wherein said amount is less than 0.5 mg/kg/day.

18. Use of dtmp for the manufacture of a sustained-release formulation, for use in the treatment of a human subject having a disorder capable of treatment using methylphenidate, wherein the amount of dtmp administered provides a serum level thereof of 16 to 140 ng.h/ml.

Patentansprüche

1. Formulierung von *d-threo*-Methylphenidat (dtMP) zur verzögerten Freisetzung.

2. Formulierung nach Anspruch 1, welche hinsichtlich einer langsameren Auflösung dem NF-Arzneiwirkstoff-Freisetzungsprofil für Methylphenidat-Hydrochlorid entspricht oder es übertrifft.

3. Formulierung nach Anspruch 1 oder Anspruch 2, welche weniger als 20 mg dtMP pro Dosierungseinheit umfasst.

4. Formulierung nach Anspruch 3, welche weniger als 15 mg dtMP pro Dosierungseinheit umfasst.

5. Formulierung nach irgendeinem der Ansprüche 1 bis 4, ausgewählt aus denjenigen, welche eine lösliche, erosionsfähige oder auf andere Weise modifizierte Beschichtung umfassen, und denjenigen, welche eine unlösliche Beschichtung aufweisen, durch die das dtMP bei der Anwendung hindurchtritt.

6. Formulierung nach irgendeinem der Ansprüche 1 bis 5, in welcher das dtMP mikronisiert ist.

7. Formulierung nach irgendeinem der Ansprüche 1 bis 6, welche (im Mittel) bei Verabreichung an (eine Stichprobe) gesunde(r) Individuen über eine Zeitspanne von mindestens 8 h einen dtMP-Serumspiegel von mindestens 50% des C_{max}-Werts aufweist.

8. Formulierung nach Anspruch 7, bei welcher die Zeitspanne 8 bis 12 h beträgt.

9. Formulierung nach Anspruch 7 oder Anspruch 8, bei welcher der Serumspiegel nach 12 bis 16 h weniger als 25% des C_{max}-Werts beträgt.

10. Formulierung nach irgendeinem der Ansprüche 1 bis 9, welche bei Verabreichung in einer Dosis von mindestens 2 mg an ein gesundes Individuum einen C_{max}-Wert von 2 bis 20 ng/ml aufweist.

11. Formulierung nach irgendeinem der Ansprüche 7 bis 10, bei welcher der C_{max}-Wert durch Kauen im wesentlichen unbeeinflusst ist.

12. Verwendung von dtMP zur Herstellung eines Medikaments zur Verwendung bei der Behandlung eines Individuums, das eine Störung aufweist, die einer Behandlung unter Verwendung von Methylphenidat zugänglich ist, einer Formulierung zur verzögerten Freisetzung, umfassend dtMP in einer ausreichenden Menge, um einen Serumspiegel von mindestens 50% des maximalen Spiegels für mindestens 8 h aufrechtzuerhalten.

13. Verwendung nach Anspruch 12, bei welcher mindestens die Anfangsdosis weniger als 15 mg dtMP pro Tag beträgt.

14. Verwendung nach Anspruch 12 oder Anspruch 13, bei welcher das Individuum erwachsen ist und die Störung Kaufzwang, Narkolepsie oder Schlafsucht ist.

15. Verwendung nach Anspruch 12 oder Anspruch 13, bei welcher die Störung das hyperaktive Syndrom ist.

16. Verwendung nach irgendeinem der Ansprüche 12 bis 15, bei welcher die Menge weniger als 1 mg/kg/Tag beträgt.

17. Verwendung nach Anspruch 16, bei welcher die Menge weniger als 0,5 mg/kg/Tag beträgt.

18. Verwendung von dtMP zur Herstellung einer Formulierung zur verzögerten Freisetzung für die Verwendung bei der Behandlung eines menschlichen Individuums, das eine Störung aufweist, welche einer Behandlung unter Verwendung von Methylphenidat zugänglich ist, wobei die verabreichte Menge an dtMP für einen diesbezüglichen Serumspiegel von 16 bis 140 ng.h/ml sorgt.

Revendications

1. Préparation à libération prolongée de d-threo-méthylphénidate (dtmp).

2. Préparation selon la revendication 1, qui satisfait ou dépasse, en termes de dissolution retardée, le profil de libération d'un médicament de NF pour le chlorhydrate de méthylphénidate.

3. Préparation selon la revendication 1 ou la revendication 2, qui comprend moins de 20 mg de dtmp par dose unitaire.

4. Préparation selon la revendication 3, qui comprend moins de 15 mg de dtmp par dose unitaire.

5. Préparation selon l'une quelconque des revendications 1 à 4, choisie parmi celles comprenant un revêtement soluble, érodable ou modifié d'une autre manière, et celles présentant un revêtement insoluble que traverse le dtmp, en utilisation.

6. Préparation selon l'une quelconque des revendications 1 à 5, dans laquelle le dtmp est micronisé.

7. Préparation selon l'une quelconque des revendications 1 à 6, qui (en moyenne), lorsqu'elle est administré à des (un échantillon de) sujets sains, présente une teneur en dtmp dans le sérum d'au moins 50% C_{max}, sur une période d'au moins 8 heures.

8. Préparation selon la revendication 7, dans laquelle la période est de 8 à 12 heures.

9. Préparation selon la revendication 7 ou la revendication 8, dans laquelle la teneur dans le sérum est inférieure à 25% C_{max} après 12 à 16 heures.

10. Préparation selon l'une quelconque des revendications 1 à 9 qui, lors de l'administration à un sujet sain, présente un C_{max} de 2 à 20 ng/ml à un dosage d'au moins 2 mg.

11. Préparation selon l'une quelconque des revendications 7 à 10, dans laquelle C_{max} est essentiellement non affecté par la mastication.

12. Utilisation de dtmp pour la fabrication d'un médicament à utiliser dans le traitement d'un sujet présentant un trouble pouvant être traité en utilisant du méthylphénidate, une préparation à libération prolongée comprenant du dtmp en quantité suffisante pour maintenir une teneur dans le sérum d'au moins 50% de la teneur maximale, pendant au moins 8 heures.

13. Utilisation selon la revendication 12, dans laquelle au moins la dose initiale est inférieure à 15 mg de dtmp par jour.

14. Utilisation selon la revendication 12 ou la revendication 13, dans laquelle le sujet est un adulte et le trouble est le trouble de l'achat compulsif, une narcolepsie ou une hypersomnie.

15. Utilisation selon la revendication 12 ou la revendication 13, dans laquelle le trouble est le trouble de l'hyperactivité avec déficit de l'attention.

16. Utilisation selon l'une quelconque des revendications 12 à 15, dans laquelle la dite quantité est inférieure à 1 mg/kg/jour.

17. Utilisation selon la revendication 16, dans laquelle la dite quantité est inférieure à 0,5 mg/kg/jour.

18. Utilisation de dtmp pour la fabrication d'une préparation à libération prolongée, à utiliser dans le traitement d'un patient humain présentant un trouble pouvant être traité en utilisant du méthylphénidate, dans laquelle la quantité de dtmp administrée assure une teneur de celui-ci dans le sérum de 16 à 140 ng.h/ml.

Chart 1

Comparison of AUC for d-isomer; d-isomer vs racemate dosing

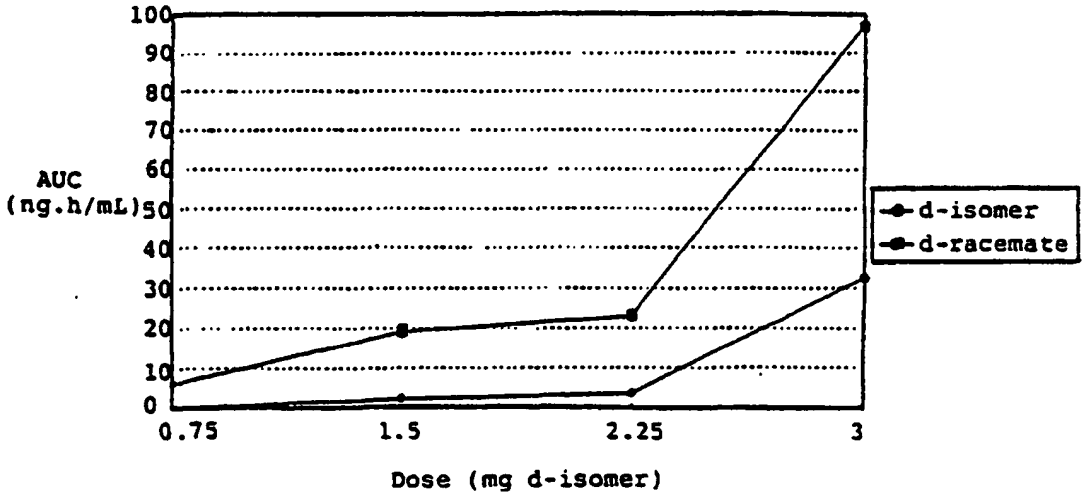

FIG. 1